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TITLE: Development of a Paracorporeal Pump-Integrated Artificial Lung for Transport of Warfighters with Acute Respiratory Distress Syndrome (ARDS)

PRINCIPAL INVESTIGATOR: Dongfang Wang, MD, PhD

CONTRACTING ORGANIZATION: University of Kentucky, Lexington, KY

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6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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14. ABSTRACT
Our goal is to develop a pump-integrated artificial lung (pPIAL) device for the safe warfighter transfer from combat theaters to regional medical centers. This one-piece compact pPIAL allows attachment to the patient body (paracorporeal) to enable easy deployment in the battlefield setting. In this first year of the DoD grant, we utilized computational fluid dynamics (CFD) simulation to refine the original design, not only for least potential of blood damage and thrombogenicity, but also for best performance of pumping and oxygenation. Based on the refined design, we established the technique/methodology to fabricate a high quality, complete working pPIAL system prototype, including the artificial lung, integrated pneumatic pump, and pneumatic pump console. Using this fabrication methodology, we made an initial pPIAL system prototype. Our first year solid achievements smooth the continuation of next two years proposed research, including in vitro bench testing and long-term animal evaluation. Due to the simpler, paracorporeal circuit, the pPIAL system will be easily deployed in the battlefield. The considerably shorter blood tubing connection will make the transport of ARDS warfighters much safer. The combined rapid deployment of respiratory support and safe transport for more comprehensive treatment will likely decrease ARDS mortality in these soldiers.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Acute respiratory distress syndrome (ARDS) significantly contributes to combat casualty and has a high mortality rate. Extracorporeal lung support is needed for ARDS warfighter transport from combat theaters to regional medical centers. A venovenous extracorporeal membrane oxygenation (vv ECMO) system was previously used, but it was bulky/complicated with a blood pump, an artificial lung (AL), and their individual control systems, requiring remote positioning with very long connection tubing. **Our objective** is to develop a paracorporeal pump-integrated artificial lung (pPIAL) device to replace separate AL and bulky pump. This one-piece compact pPIAL allows direct attachment to the patient's body, eliminating the long tubing connection. In **Specific Aim 1**, pPIAL and pneumatic console working prototypes will be developed and fabricated. The pPIAL consists of a compact AL and an integrated pump. The pneumatic console drives the pump and supplies the sweep gas. This design will be fine-tuned with computational fluid dynamics. In **Specific Aim 2**, the *in vitro* gas exchange efficiency and pump performance of the pPIAL will be evaluated. In **Specific Aim 3**, the *in vivo* performance of the pPIAL in sheep will be evaluated. The pPIAL circuit will consist of the pPIAL prototype, the AvalonElite double lumen cannula, and a short blood tubing connection. This circuit will be tested in sheep for 6 hrs (N=10) and for 2 weeks (N=10). The new, simple pPIAL can be easily deployed on the battlefield, and the much shorter blood tubing connection makes ARDS warfighters transport much safer.

2. KEYWORDS:

acute respiratory distress syndrome (ARDS), paracorporeal pump-integrated artificial lung (pPIAL), extracorporeal membrane oxygenation (ECMO), sheep

3. ACCOMPLISHMENTS:

Specific Aim 1: To Develop and Fabricate a pPIAL Working Prototype with Pneumatic Console	**Time**	**Status**
Major Task 1: Initial redesign and fabrication preparation of pPIAL and pneumatic console	Month	
Milestone(s) Achieved:		
Finish first version of design blue print.	6th	Complete
Finish initial CFD simulation.	6th	Complete
Determine the detailed fabrication process and purchase main materials, parts, and supplies for fabrication.	6th	Complete
Major Task 2: Fabrication of first working prototype of pPIAL and pneumatic console for initial bench test to identify any major flaws		
Milestone(s) Achieved:		
Fabricate first working pPIAL prototype	12th	Complete
Finish CFD simulations	12th	Complete
Fabricate first working pneumatic console prototype	12th	Complete
Major Task 3: Fabrication of working prototype of pPIAL and pneumatic console for full bench test and short-term *in vivo* sheep test		
Milestone(s) Achieved:		
Fabricate working pPIAL prototypes	24th	Complete
Finalize CFD simulation	24th	95% Complete
Fabricate working pneumatic console prototypes	24th	Complete
Major Task 4: Fabrication of mature of pPIAL and pneumatic console prototypes for long term animal test		
Milestone(s) Achieved:		
Finish mature pPIAL and pneumatic console prototypes for long term animal study	36th	
Specific Aim 2: To Evaluate pPIAL *in vitro* Gas Exchange Efficiency and Pump Performance	**Time**	**Status**
Major Task 1: Initial bench test with 37% glycerin	Month	
Milestone(s) Achieved:		
Finish design of benchtop mock loop	3rd	Complete
Finish assembly of benchtop mock loop	6th	Complete
Finish initial bench test	12th	Complete
Major Task 2: Finish full short-term benchtop test with bovine blood		
Milestone(s) Achieved:		
Finish bench test for pPIAL pump/gas exchange performance and bio- compatibility test. Identify potential problems for prototype modification.	20th	25% Complete
Major Task 3: Finish one month pPIAL durability benchtop test with 37% glycerin		
Milestone(s) Achieved:		
Finish long-term pPIAL durability benchtop test with 37% glycerin	24th	25% Complete

Specific Aim 3: To Evaluate the in vivo Performance of pPIAL in Sheep	**Time**	**Status**
Major Task 1: IACUC/ACURO protocol approval	Month	
Milestone(s) Achieved		
IACUC Approval	8th	Complete
ACURO Approval	9th	Complete
Major Task 2: Perform short-term in vivo sheep study	Month	
Milestone(s) Achieved		
Finish short term in vivo sheep study	30th	
Major Task 3: Perform long-term in vivo sheep study	Month	
Milestone(s) Achieved		
Finish long-term in vivo sheep study	36th	

What was accomplished under these goals?

A. Year 1 Accomplishments

In the First 12 months, the following Major Tasks have been completed:

- Specific Aim 1 Major Tasks 1 and most of Major Task 2
- Specific Aim 2 Most of Major Task 1
- Specific Aim 3 Major Task 1

In summary, the following achievements have been accomplished:

1. The first pPIAL computational fluid dynamics (CFD) investigation has been completed with the following pump-lung geometry (**Fig 1**)
   - Fiber bundle height ~60 mm
   - Bundle outer diameter ~ 85 mm
   - Bundle inner diameter ~ 38 mm
   - Assume fiber bundle porosity of 0.5
   - Total surface area 1.434 m^2

   The CFD simulation showed a relatively even blood flow distribution inside the first pPIAL prototype (**Fig 2**).

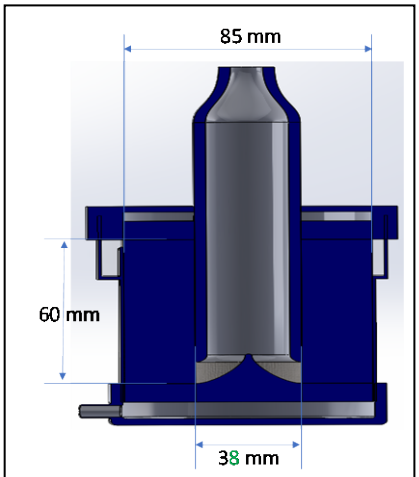

Fig 1: The pPIAL geometry for the first CFD simulation

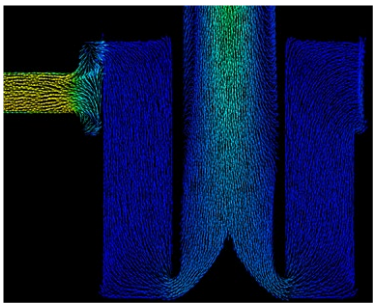

Fig 2: CFD showing the relatively even flow distribution of the first pPIAL prototype

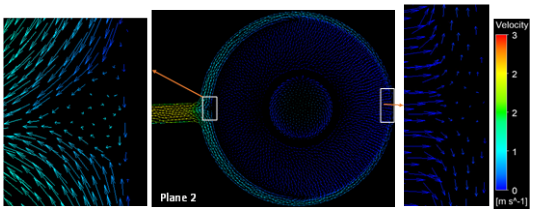

Fig 3: Two potential problems were identified in pPIAL outlet flow pattern.

However, two potential problems were identified in the pPIAL outlet flow pattern (**Fig 3**).

1) Potential stagnant flow in rear pPIAL outlet
2) Potential stagnant flow in front outlet

2. Three working prototypes were fabricated and tested (**Fig 4, Table 1**)

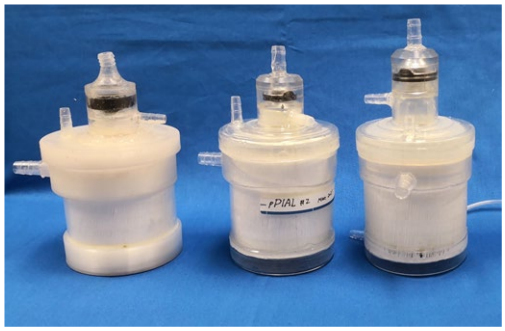

Fig 4: Three pPIAL working prototypes were fabricated.

Table 1: Previous 3 Prototypes Fabrication Parameters and *in vitro* Performance

	Prototype 1	Prototype 2	Prototype 3
Fiber type	Polypropylene 30/240	Poly-Methylpentene 90/200	Poly-Methylpentene 90/200
Fiber ID (mm)	0.24	0.2	0.2
Fiber OD (mm)	0.30	0.38	0.38
Fiber height (mm)	60	60	63
Fiber amount	25358	24140	24140
Total Surface (m^2)	1.434	1.729	1.816
Bundle OD (mm)	85	85	85
Bundle ID (mm)	38	38	40
Oxygenator priming volume (ml)	95	95	101
O_2 transfer (ml/min)	146	160	171
CO_2 removal (ml/min)	149	352	543
Max pumping flow (L/min)	2.91	2.75	3.20

The major problem of the above 3 pPIAL prototypes was that the pumping flow was under 3.2 L/min due to valve regurgitation and an inefficient pPIAL controller.

B. Year 2 Accomplishments

In the last 2 years, the following Major Tasks have been completed:

- Specific Aim 1 Major Task 1, 2, and 3
- Specific Aim 2 Major Task 1
- Specific Aim 3 Major Task 1

The summary of Year 2 major accomplishment:

1. Used CFD to further optimize the pPIAL flow pattern:
   a. New blueprint/geometry (**Fig 5**):

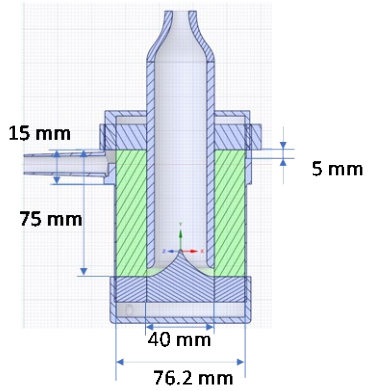

Fig 5: New blueprint for CFD and prototyping.

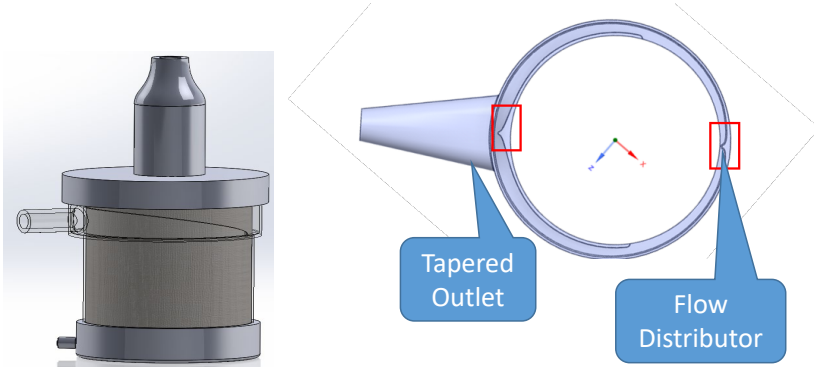

Fig 6: A flow distributer and a tapered outlet was added to address uneven blood flow in the PIAL outlet end

   b. Optimize pPIAL uneven blood flow pattern.
   A flow distributer and a tapered outlet was added to address the uneven blood flow in the pPIAL outlet end (**Fig 6**). The CFD simulation demonstrated that the rear stagnant flow is addressed by flow distributer, but 2 outlet vortexes were present (**Fig 7**).

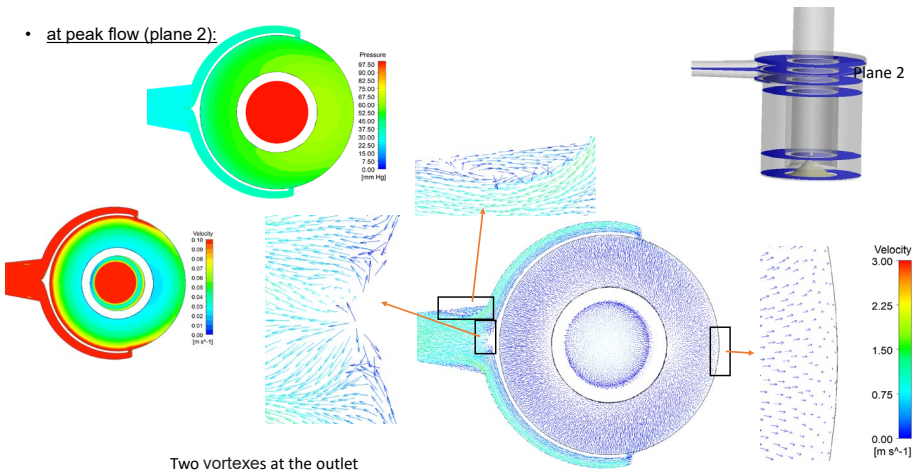

Fig 7: The flow distributer resolved stagnant flow problem, but there were 2 outlet vortexes.

2. Most Recent pPIAL prototypes system (**Fig 8**):

a. Digital pPIAL controller (previously called Pneumatic Console): Our updated pPIAL controller featured:
   i. Very compact size (22x20x16 cm)
   ii. 7 inch touch screen for control and monitor
   iii. Significantly improved performance by upgraded internal pneumatic connection:
      (a) copper tubing (7.7 mm ID) to replace previous polypropylene tubing (4.5 mm ID),
      (b) ¼ inch electric magnetic valve to replace small 1/8 inch electric magnetic valve.

b. The pPIAL prototype: Our most recent 5th pPIAL prototype is significantly smaller than the previous version with 1. 5 M^2 surface area (Polymethylpentene hollow fiber).

c. Used ball valve to replace disk valve for less regurgitation.

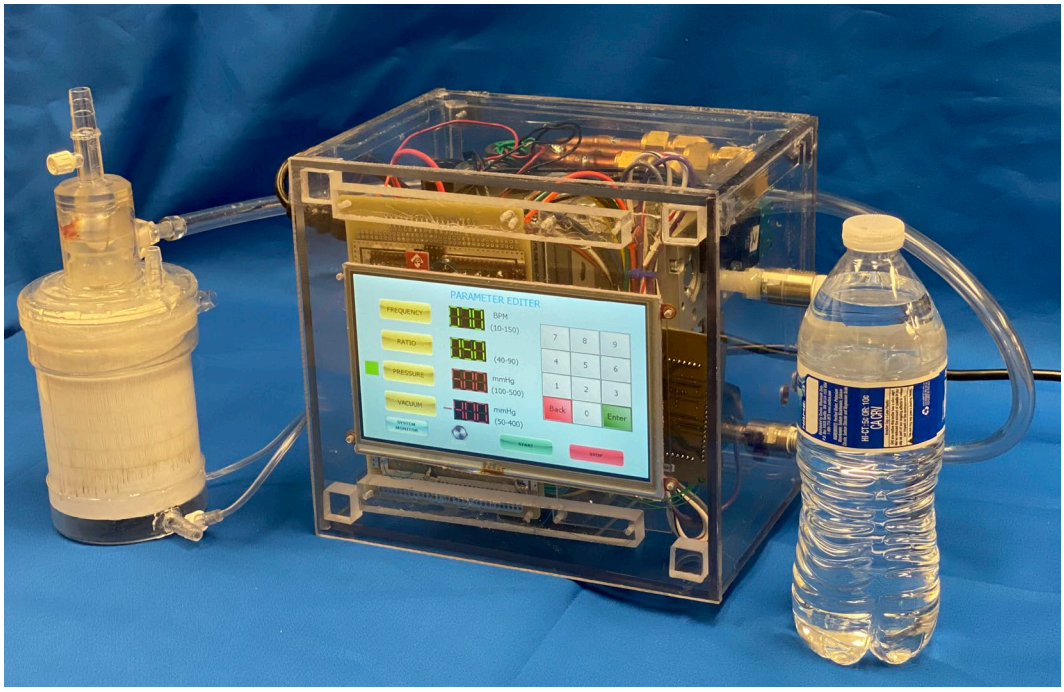

Fig 8: Very compact size of latest pPIAL system prototype.

The 4th and 5th pPIAL prototypes have been fabricated according to the latest blueprint. The 5th prototype is smaller with 1.5 M^2 surface area polymethylpentene hollow fiber (**Fig 9**). Prototype 4 and 5 achieved over 4 L/min pumping blood flow due to an improved pPIAL controller and less regurgitation with ball valves (**Table 2**).

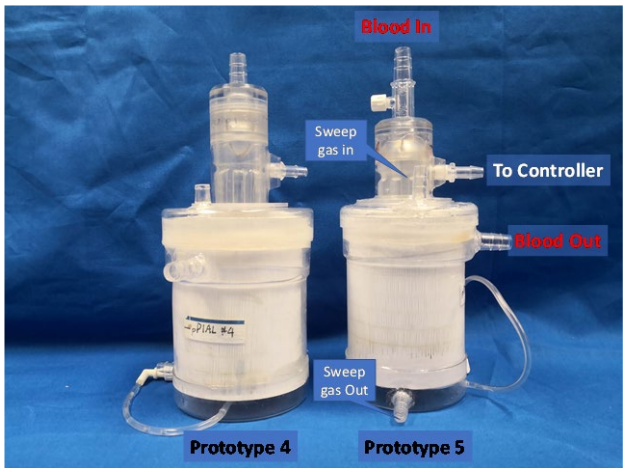

Fig 9: The pPIAL prototypes 4 & 5

Table 2: Prototype 4 & 5 Fabrication Parameters and *in vitro* Performance		
	Prototype 4	Prototype 5
Fiber type	Poly-Methylpentene 90/200	Poly-Methylpentene 90/200
Fiber ID (mm)	0.2	0.2
Fiber OD (mm)	0.38	0.38
Fiber height (mm)	85	75
Fiber amount	25481	17166
Total Surface (m^2)	2.586	1.537
Bundle OD (mm)	85	76
Bundle ID (mm)	40	40
Oxygenator Priming volume (ml)	118	92
O_2 transfer (ml/min)	250	223
CO_2 removal (ml/min)	473	342
Max pumping flow (L/min)	4.11	4.05

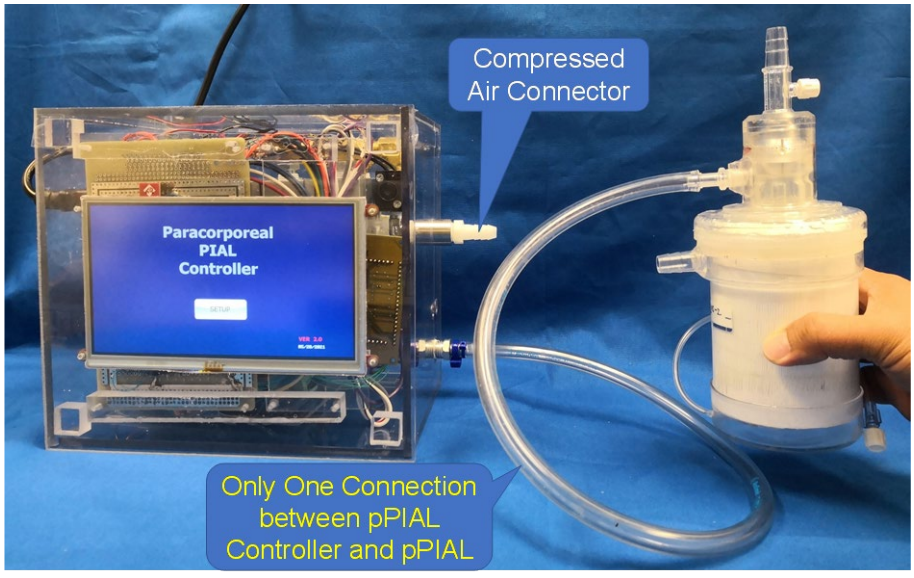

Fig 10: Only one connection between the pPIAL controller and the pPIAL

In summary, our pPIAL is very small and easily amenable for paracorporeal positioning with potential ambulation. The compact controller only has one pneumatic tubing (not blood tubing as in current ECMO) that connects to the pPIAL, making it a safe paracorporeal artificial lung system for long distance war fighter transportation (**Fig 10**).

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

An abstract with the pPIAL prototype fabrication, CFD analysis, and bench testing results was accepted for a poster presentation at the 2021 MHSRS meeting. Unfortunately, this meeting was cancelled due to COVID-19 concerns.

What do you plan to do during the next reporting period to accomplish the goals?

Optimize design to eliminate the 2 outlet vortexes
In vitro blood compatibility and 37% glycerin durability test
Short-term animal testing

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Short-Term Impact: The short-term impact will be the development of a new simple and reliable pPIAL system with proven gas exchange efficiency and pump performance. This will lay the foundation for GLP animal studies for FDA investigational device exemption (IDE) approval for clinical trials and the eventual completion of clinical trials for FDA approval for clinical use in ARDS patients. **Long-Term Impact:** Due to the simpler, paracorporeal circuit, the pPIAL system will be easily deployed in the battlefield setting. The considerably shorter blood tubing connection will also make the transport of warfighters with ARDS from combat theaters to regional medical centers much safer. The combined rapid deployment of respiratory support and safe transport will likely decrease the mortality of acute lung injury in these soldiers.

What was the impact on other disciplines?

Our pPIAL circuit may also pave the way for a truly ambulatory respiratory support system to enhance the recovery of chronic lung disease patients from acute exacerbation and to improve end stage lung disease patients' physical condition for better lung transplant outcomes.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

None

Actual or anticipated problems or delays and actions or plans to resolve them

Biocompatibility Testing
Initial biocompatibility testing showed that the bovine blood purchased from a company in Tyler, Texas had unacceptably high levels of hemolysis. The company acknowledged the high levels of hemolysis in their bovine blood samples obtained from a slaughterhouse. We will pursue 2 options to address this problem. First, we can order bovine blood from this same company, but use a donor cow instead, which has proven lower hemolysis. Second, we can use fresh sheep blood from our acute in vivo sheep experiments.

37% Glycerin Durability Testing
We will do the durability testing on a higher quality prototype after the acute sheep studies.

Changes that had a significant impact on expenditures

None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Not applicable, no human subject studies proposed in this project.

Significant changes in use or care of vertebrate animals

There have been no significant changes in the use or care of vertebrate animals.

Significant changes in use of biohazards and/or select agents

Not applicable, no hazards or select agents will be used in this project.

6. PRODUCTS:

- ## Publications, conference papers, and presentations

Journal publications.

Nothing to report. This project is in the early stage of device fabrication and bench testing.

Books or other non-periodical, one-time publications.

Nothing to report. This project is in the early stage of device fabrication.

Other publications, conference papers and presentations.

An abstract was accepted for poster presentation at the 2021 MHSRS meeting:

Wang D, Ballard-Croft C, Zhuang Z, Shao Z, Li L, Zwischenberger JB. Development of a Paracorporeal Pump-Integrated Artificial Lung to Facilitate the Safe Transport of Warfighters with Life-threatening Respiratory Failure from the Battlefield to a Regional Medical Center. Abstract #21-04559 (Accepted at MHSRS 2021).

Unfortunately, this meeting was cancelled due to COVID-19 concerns.

- ## Website(s) or other Internet site(s)

Nothing to report.

- ## Technologies or techniques

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to report. The Principal Investigator (DW) and a Co-Investigator (JZ) already have a patent for the technology to be developed in this project.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Dongfang Wang, MD, PhD
Project Role: Principal Investigator
Nearest person month worked: 7
Contribution to Project: Dr. Wang led efforts on pPIAL design/fabrication and the *in vitro* bench testing set-up/performance. He also provided supervision/insight on parts and supplies purchases for fabrication.
Name: Joseph Zwischenberger, MD
Project Role: Co-Investigator
Nearest person month worked: 2
Contribution to Project: Dr. Zwischenberger provided key input regarding the pPIAL design.
Name: Cherry Ballard-Croft, PhD
Project Role: Co-Investigator
Nearest person month worked: 7
Contribution to Project: Dr. Ballard-Croft assisted with pPIAL fabrication parts/supplies purchases, *in vitro* bench testing set-up/performance, and IACUC protocol submission and revision, and IACUC inspection of sheep lab.
Name: Michael Sekela, MD
Project Role: Co-Investigator
Nearest person month worked: 0.1
Contribution to Project: Dr. Sekela provided input on the pPIAL design from a cardiothoracic surgeon's perspective.
Name: Vincent Sorrell, MD
Project Role: Co-Investigator
Nearest person month worked: 0.2
Contribution to Project: Dr. Sorrell advised on the logistics of echocardiography in sheep.
Name: Peter Morris, MD
Project Role: Co-Investigator
Nearest person month worked: 0.1
Contribution to Project: Dr. Morris provided input on pPIAL design from pulmonologist's perspective.
Name: Stephen Topaz, BSE
Project Role: Co-Investigator
Nearest person month worked: 2
Contribution to Project: Mr. Topaz supervised the pPIAL design and fabrication.
Name: Zhongjiang Zhuang, BSE, MS
Project Role: Co-Investigator
Nearest person month worked: 11
Contribution to Project: Mr. Zhuang worked on pPIAL pump/console fabrication and bench test set-up.
Name: Zeng Shao, BS, MS
Project Role: Engineer
Nearest person month worked: 12
Contribution to Project: Mr.Shao assisted with pPIAL pump/console fabrication and bench test set-up.
Name: Li Li, MD
Project Role: Post-Doctoral Scholar
Nearest person month worked: 10
Contribution to Project: Dr. Li assisted with design/set-up of bench test and performed bench test with bovine blood. He also analyzed the data and performed the O2 transfer/CO2 removal calculations.

Name: Amal Alotaibi, MD
Project Role: Post-Doctoral Scholar
Nearest person month worked: 9
Contribution to Project: Dr. Alotaibi assisted with the set-up of the bench test and performed bench test with bovine blood. She also assisted with data analysis and O2 transfer/CO2 removal calculations.
Name: Yulin Zhang, MS
Project Role: Graduate Student
Nearest person month worked: 8
Contribution to Project: Ms. Zhang performed the 3D design and digital 3D printing of pPIAL parts. She also explored the potential of particle image velocimetry (PIV) for validation of CFD results.
Name: Zongjun Wu, PhD
Project Role: Principal Investigator of Subcontract
Nearest person month worked: 1
Contribution to Project: Dr. Wu directed preparation for final CFD simulations of fine-tuned, optimized pPIAL design.
Name: Jiafeng Zhang, PhD
Project Role: Research Associate of Subcontract
Nearest person month worked: 2
Contribution to Project: Dr. Zhang collected information to prepare for final CFD simulations of fine-tuned, optimized pPIAL design.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

A new NIH Phase I SBIR grant subcontracted to the University of Kentucky was awarded on 04/01/2021. The PI (DW) and Co-Is (JZ, CBC, ST) receive funding from this grant.

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not Applicable

QUAD CHARTS: Not Applicable

9. APPENDICES:

PR181510: Development of a Paracorporeal Pump-Integrated Artificial Lung for Transport of Warfighters with Acute Respiratory Distress Syndrome (ARDS)

PI: Dongfang Wang, University of Kentucky, KY
Budget: $3,906,819.00
Topic Area: Technology/Therapeutic Development
Mechanism: W81XWH18PRMRPTTDA

Research Area(s): SCS Coding:1600
Award Status: Year 2: 08/15/2020-08/14/2021

Study Goals:

Our ultimate goal is to develop a simple lung support system with no need of long blood tubing connection for the safe ARDS warfighter transfer from combat theaters to regional medical centers. **Our objective** is to design one device (pPIAL) to replace separate AL and bulky pump. This one-piece compact pPIAL allows attachment to patient body (paracorporeal/wearable), eliminating the long tubing connection and associated high blood resistance/trauma and mitigating cannula dislodgement/catastrophic cannula decannulation.

Specific Aims:

Specific Aim 1: To Develop and Fabricate a pPIAL Working Prototype with Pneumatic Console. In this specific aim, a pPIAL and its console will be developed. The pPIAL will consist of an AL and an integrated pump.

Specific Aim 2: To Evaluate pPIAL *in vitro* Gas Exchange Efficiency and Pump Performance. In this specific aim, the pPIAL prototype will be bench tested in a mock circuit for its pump and gas exchange performance.

Specific Aim 3: To Evaluate the in vivo Performance of pPIAL in Sheep: In this specific aim, the paracorporeal AL circuit will consist of the pPIAL prototype, the AvalonElite® double lumen cannula, and short blood tubing connection. This circuit will be tested in sheep for 6 hours (n=10) and for 2 weeks (n=10) to evaluate pPIAL *in vivo* gas exchange and pump performance.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date

1) Finished all CFD simulations. 2) Finalized the pPIAL blueprint. 3) An updated pPIAL system comprised of compact pPIAL and pneumatic console prototypes were fabricated and tested, showing over 4 L/min pumping flow and good gas exchange performance.